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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | | ATTORNEY DOCKET NO. |
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| 09/082,112 | 05/20/98 | MENDOZA | A | MSU4.1-406 |

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| **ART UNIT** | **PAPER NUMBER** |
| 1645 | 6 |

**DATE MAILED:** 07/21/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/082,112 | Applicant(s) Mendoza |
|---|---|---|
| | Examiner Sharon L. Turner, Ph.D. | Group Art Unit 1645 |

☒ Responsive to communication(s) filed on *6-25-99* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *16-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). (2)

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The preliminary amendment originally filed 5-20-98 has been entered. Claims 1-15 have been canceled. Claims 16-25 are pending.

### *Election/Restriction*

2. Applicant's election with traverse of Group I in Paper No. 5 is acknowledged. The traversal is on the grounds that the restriction was inconsistent with the parent case and that claims 1-15 had been canceled. This argument is persuasive. The preliminary amendment has been entered and claims 16-25 will be examined.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The specification is objected to under 35 USC § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. *Pythium insidiosum* is required to practice the claimed invention. Although a deposit of this organism has been made, the necessary criteria of the deposit rules under the Budapest Treaty have not been met. The specification lacks a date of deposit and the address of the depository has changed. An affidavit or declaration by Applicants,

or statement by an attorney of record stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.801-37 CFR 1.809.

5. Claims 16-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification describes page 6, line 15, the improved vaccine (was) prepared by adding cytoplasmic antigens to the earlier *P. insidiosum*-vaccine (Mendoza et al., Mycopathologica 119:89-95 (1992(a))). However, Mendoza et al, 1992(a) disclose two vaccines, cell-mass (CMV) and soluble concentrated antigen (SACV). (1) The specification does not specify to which vaccine the cytoplasmic antigens were added. (2) In addition, neither of the vaccines of Mendoza et al., 1992(a) disclose the method of the instant invention as directed in Example 1. For example neither the CMV or SACV vaccine comprise step 3 of Example 1, which states the cultures were killed with Merthiolet (thimerosal) (0.02% wt/vol), filtered to separate the cells (hyphae) from the liquid phase containing exoantigens of *P. insidiosum* (save the liquid phase in a sterile container to be used in step 6). (3) The specification does not teach the efficacy of the CMV or SACV antigens and does not teach the preparation or addition of cytoplasmic antigens to these vaccines. (4) The structure of the cytoplasmic antigens is described only by reference to Mendoza et al., J. Clin. Microbiol., 30:2980-2983, 1992(b). As

discussed, the specification states that the addition of cytoplasmic antigens provides the improved vaccine. Mendoza et al., 1992(b), describe 20 different antigens detected by sera of horses with Pythiosis. Yet, the specification Example 1, step 6 designates that a mixture of (the) three proteins were added to Mendoza's original vaccine. The specification does not provide guidance for which antigens of the 20 provide the improved vaccine, only that a mixture of three were added. In addition, the amount of each is not specified. As vaccination is a highly unpredictable art and one of skill would not possess the knowledge to determine the amounts or which 3 of the 20 antigens provide therapeutic effects. Thus, the disclosure as written is not considered to be enabling. Without further experimentation one of skill in the art could not reasonably be assured of making or practicing the vaccine of instant invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 16 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16 and 18 recite methods of treating Pythiosis, yet it is unclear which steps comprise the method other than providing the vaccine. It is further unclear what composition the vaccine is providing. Does the admixture contain elements (1) and (2)? Does the admixture contain 1 or more intracellular and extracellular proteins? What is meant by

extracellular proteins? Extracellular proteins could refer to cell membranes, isolated glycoproteins, cell surface proteins, the growth media etc. How does the composition of claim 16 differ from the composition of claim 18 or are they the same? How are the proteins separated and identified; i.e. by molecular weight, immunoreactivity.

8. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The grammar of claim 19 renders it indefinite; i.e., has the second supernatant been separated, by what technique, providing what potential benefit to the vaccine? How has the first supernatant been separated? Does each fraction constitute an admixture? Are the two fractions later combined? How can the procedure of claim 19 depend on the procedure of claim 18 since they each provide distinct vaccine procedures, i.e. Does the method of claim 19 kill cells with thimersol and then separate according to claim 18 or is the method of claim 19 performed after the cells have already been separated?

***Claim Rejections - 35 USC § 102 or 103***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 18, 20-22, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI).

Claim 18 recites a method for the effective treatment by subcutaneous vaccination of Pythiosis in a mammal having the disease which comprises: (a) providing an injectable vaccine which comprises in a sterile aqueous solution in admixture: (1) (of) an intracellular proteins separated from disrupted cells of *Pythium insidiosum*; and (2) extracellular proteins from a

supernatant from growing the cells of the *Pythium insidiosum*; and (b) vaccinating the mammal with the vaccine.

Claim 20 recites the method of claim 18 wherein the cells have been disrupted by sonication.

Claim 21 recites the method of claim 18 wherein the *Pythium insidiosum* is deposited as ATCC 58643.

Claim 22 recites the method of any one of claims 19, 20 or 21 wherein the culture medium is Sabouraud dextrose broth.

Claim 24 recites the method of claim 19 wherein the disrupted cells are separated from the culture medium for the cells by centrifugation.

Mendoza et al, 1992 teach two vaccines for Pythiosis. The first, page 90, column 2, Vaccine production, comprises inoculation and growth of *P. insidiosum* in Sabouraud dextrose broth, (claim 22), followed by filtration through a Whatman No. 40 filter paper, claim 18(b). The fungal mass was then washed three times with 200 ml of 0.75% of NaCl solution. In the last wash, the cell-mass was resuspended in 15 ml of sterile saline solution and then broken in a Braum MSK cell homogenizer, until microscopically 80% of the hyphae were observed to have been fragmented. This step effectively separates or releases the intracellular proteins from the cell material, claim 18(1) and therefore provides an admixture of intracellular and extracellular proteins, claim 18(a). The hyphae were transferred to a container, desicated and the final dose was adjusted to 5 mg dry weight/ml with 5% phenolized, sterile saline (an aqueous) solution,

claim 18. Homogenization breaks cells open and is inherently deemed to provide no difference from sonication, claim 20. As described on page 89, column 1, line 12 Introduction, Mendoza et al., have found that nine Pythium strains isolated from humans, horses and dogs with active pythiosis belonged to the same species, teaching that *P. insidiosum* is inherently equivalent to ATCC 58643, claim 21. *P. insidiosum* 58643 was used in the production of the CMV vaccine, page 90, Vaccine production. The CMV procedure utilizes centrifugation for the cell washes, claim 24. The beneficial results of the CMV vaccine are illustrated in Tables 1-3.

12. Claims 16-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza et al, J. Mycol. Med, 1996, 6:151-164. Claims 18, 20-22 and 24 are set forth above.

Claim 16 recites a method for treatment of Pythiosis in human patients having the disease which comprises: (a) providing a vaccine containing separated proteins of *Pythium insidiosum* in a sterile aqueous solution; and (b) vaccinating the patient with the vaccine.

Claim 17 recites the method of claim 16 wherein the vaccination is subcutaneous.

Claim 19 recites the method of claim 18 wherein the proteins have been provided by growing cells of the *Pythium insidiosum* in a culture medium, then killing the cells, then separating the killed cells from the culture medium to produce a first supernatant and then disrupting the cells in water to provide the intracellular proteins in a second supernatant which have separated and (2) separating the extracellular proteins from the first supernatant.

Claim 23 recites the method of claim 19 wherein the cells are killed with thimersol.

Claim 25 recites the method of claim 19 wherein the separated proteins have been precipitated together from the first and second supernatant combined together using acetone and then dispensed in sterile distilled water to provide the vaccine.

Mendoza et al, 1996 teach the prevalence of human pythiosis infection and a need for effective human vaccines, page 156, column 2. Mendoza et al, 1996, also teach the benefits of vaccination using antigens derived from *P. insidiosum*, see page 158, column 1, lines 5-8, 24 and Immunotherapy, page 161-162 with reference to the vaccine treatments of IDS:References AB, AC, AD, AH, AI and AJ. Mendoza et al, 1996, teach that the addition of cytoplasmic antigens, contining the 28K, 30K and 32K immunodominant proteins to these pythium vaccines (in reference to Mendoza, Enhancement of the therapeutic effect of a vaccine against equine pythiosis insidiosis by a hyphal antigen protein of the oomycete *Pythium insidiosum,* The Third NIAID Workshop in Medical Mycology Series. Montana, September, p.9, 1995) enhances curative properties, page 159, line 15-18. Mendoza et al teach similarilties in the recognition of Pythium antigens detected from sera of humans and horses infected with *Pythiosis insidiosum*, see page 159, Immunodiffusion test and Western Blot. Mendoza et al, 1996, however do not teach the benefit of such vaccine preparations in humans. Knowing the similarity in antigenicity and serological reactivity in humans to that found in horses, and the benefit of the described vaccines in horses, it would have been prima facie obvious to use the vaccine antigen preparations described to treat *P. insidiosum* in humans. One of skill in the art would have been motivated to do so based on the effectiveness of the vaccine in horses, a knowledge of the

similarity in mammalian immune function, the similarities in antigens and recognition by sera antibodies in humans and horses, and the need for effective treatments of such infections in humans. In addition, Mendoza et al, 1996, teach the beneficial properties of immunotherapeutic vaccines by Miller et al, IDS: Reference AC and AH and Mendoza et al, IDS:Reference AB, AD, AI and AJ. Knowing the benefit of each of these vaccine procedures it would have been prima facie obvious for one skilled in the art to combine the properties (antigens) of the two vaccines to provide improved immunoprotective effects. One of skill would have been motivated to do so knowing the benefits of each respective vaccine and the need for effective treatments for Pythiosis in humans and mammals.

13. Claims 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendoza et al, Mycopathologica, 1992, 119:89-93. Claims 18-25 are set forth above.

The second method (SACV) of vaccine preparation disclosed in Mendoza et al 1992(a) comprises the use of cultured filtrate antigens prepared by growth of *P. insidiosum*, subsequent killing of the cells with phenol (an equivalent reagent to thimersol), and concentration by 20-fold in a stir cell (Amicon Corp.) The concentrated soluble antigens were precipitated with 50 ml chilled acetone twice and centrifuged at 10,000 X g. The supernatant was drained and the precipitated antigen was resuspended in 25 ml of .75% NaCl sterile solution. Mendoza et al 1992(a), teaches the effectiveness of the SACV vaccine in Tables 1-2 and 4.

Mendoza et al 1992(a) teach the method and benefit of the CMV vaccine, as set forth above, which relies on intracellular and membrane prepared antigens, in addition to the method

and benefit of the SACV vaccine using phenol (an equivalent reagent to thimersol for antigen preparation) which relies on the presevation of whole cell antigen. Mendoza et al, however do not teach the benefit of a combined vaccine using both CMV and SACV prepared antigen. Knowing the benefical effects and efficacy of both CMV prepared antigens and SACV prepared antigens, it would have been prima facie obvious for one skilled in the art to combine the alternatively prepared antigens in a single vaccine to provide the beneficial characteristics of each. One of skill in the art would have been motivated to do so being reasonably assured that a combination of the effective components of the CMV and SACV vaccines would provide improved effects.

***Status of Claims***

14. No claims are allowed.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995.

Sharon L. Turner, Ph.D.
July 13, 1999

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